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Overview

Local Therapy, Systemic Benefit: Challenging the Paradigm of Biological Predeterminism

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ABSTRACT:
This paper briefly reviews the historical evolution of paradigms that have been purported to characterise the clinical behaviour of breast cancer, with the intention of guiding treatment approaches. Results from randomised clinical trials and the explosion of knowledge in the area of cancer biology have discredited the monolithic paradigms that had dominated thinking about breast cancer in the past. Contemporary notions of breast cancer biology recognise that, although some cancers disseminate well before becoming clinically detectable, acquisition of a metastatic phenotype can occur at any point (or not at all) in the local evolution of the tumour. As a consequence, both systemic and timely local–regional therapies can be expected to influence disease dissemination and patient survival. This is consistent with results observed in clinical trials, overviews of which indicate that prevention of four local recurrences will, on the average, prevent one death from breast cancer. Optimisation of local–regional treatment is an important goal in breast cancer management. Kurtz, J. M. (2006). *Clinical Oncology* 18, 162–165

Key words: Breast cancer, local control, paradigms, radiotherapy, survival

Introduction

At a time when the understanding of the biology of breast cancer is advancing at an unprecedented rate, it seems rather simplistic to be rehashing the issue of whether a particular paradigm might be most appropriate for framing our thinking about this disease's seemingly capricious behaviour. We would like to think that we live in an age in which blind adherence to doctrines is in decline and ideologies are viewed with increasing suspicion. So why are we still interested in paradigms when mechanisms of carcinogenesis and breast cancer progression are coming to be understood on a molecular basis [1]? Although newer techniques for identifying molecular prognostic and predictive factors may well revolutionise patient management, for the moment treatment choices for individual women are based upon rather broad generalities. Our language as clinical oncologists requires us to separate in our minds the components of locoregional and generalised disease, which interact in some poorly defined way to influence the woman's chances of survival. This artificial dichotomy is perpetuated by the fact that locoregional and systemic therapies are sometimes in the hands of different medical specialities, the proponents of which each tend to protect their own interests. The importance of locoregional treatment is supported by the observation that many women whose tumours have been surgically removed live out a normal life span without cancer recurrence, whereas there is little solid evidence of this phenomenon in the absence of surgery. But does this imply that surgery should become more and more extensive, or that intensifying this component of treatment by adding locoregional radiotherapy will necessarily improve survival rates? The importance of systemic therapy is substantiated by the observation that women with breast cancer die of metastatic dissemination and not from local tumour progression. But does this mean that the 'quality' of locoregional therapy becomes irrelevant for this reason? The logistical necessity of separating cancer therapy into locoregional and general components may foster paradigm seeking, but should not polarise us into opposed camps.

Liberating Surgery from Halstedian Shackles

Although there were a few dissenting voices [2] during the first half of the 20th century, surgical thinking was dominated by the 'Halstedian' notion that breast cancer spreads centrifugally in an orderly fashion via the lymphatic system, and thence to the systemic circulation. Thus, a maximally extensive locoregional treatment was believed to be the key factor in the cure of the disease, and techniques were devised for making breast surgery increasingly radical. Extensive postoperative radiotherapy was frequently recommended, as it was apparent that locoregional control could be improved thereby. It was assumed that increased survival rates would result from these measures. The era of randomised trials marked an end to this view of breast cancer, and new working

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hypotheses were generated and tested. Some of the first breast cancer clinical trials were designed to investigate the value of extended radical surgery, and of postoperative radiotherapy [3—5]. The disappointing results of these trials put the damper on the proponents of maximal surgery, paved the way for breast-conserving therapy, and ignited an explosion of interest in systemic therapies.

Fisher [6] was instrumental in discrediting the old ideas and establishing a new paradigm to fill the Halstedian void. On the basis of laboratory investigations into mechanisms of metastatic dissemination, Fisher concluded that 'operable breast cancer was a systemic disease involving a complex spectrum of host-tumour inter-relations…. (and that) variations in treatment of locoregional disease were unlikely to affect survival.' Patient outcome was essentially predetermined by tumour biology, and could be influenced only by agents that modified this biology. Propositions for improving therapeutic efficiency were not predicated upon increased local radicality, but 'involved treating patients who were free of identifiable metastatic disease with systemic adjuvant therapy because some of them might develop distant disease in the future…' [6]. The worth of such adjuvant therapies was to be scientifically evaluated within the framework of carefully designed randomised-controlled trials.

This paradigm shift, if one must call it that, has had a predominantly favourable effect on how breast cancer is currently treated. Adjuvant therapy received the emphasis that it deserved, contributing, to some extent, to the general improvement in rates of recurrence and survival and the reduction in breast cancer mortality observed in some developed countries in recent years [7]. A concomitant reduction in the aggressiveness of locoregional treatment lead to the current notion of breast conservation as the preferred surgical approach. There is little doubt that the new paradigm liberated surgical thinking in a positive way, allowing developments (e.g. sentinel-node biopsy) that would have been unimaginable in Halstedian terms. Many women with breast cancer have undoubtedly profited from this new mind set. However, this new paradigm has a potentially negative side. If breast cancer is to be thought of as a systemic disease, even in its early stages, then locoregional treatment decisions are relegated to a category of lesser importance. What, then, is the value of quality in breast cancer surgery, and what is the role of adjuvant radiotherapy? Is it simply a matter of minimising the disagreeable consequences of local failure? Is local control only a quality-of-life issue? Is sloppy locoregional therapy acceptable as long as optimal systemic therapy is given?

Biological Predeterminism? Yes, But…

The transformation of normal cells into cancer is a multi-step process involving many genes, and, in some tumours, the acquisition of a metastatic phenotype may indeed be an early event. However, there is nothing in modern biology that precludes the possibility that a substantial subpopulation of non-metastatic tumours might exist at any point in time. Nor does modern biology exclude the possibility that, momentarily, non-metastatic tumours might later give rise to metastases if allowed to progress locally for a longer period of time. As a reaction to the constraints imposed by 'black or white' paradigms, the 'spectrum hypothesis' of Heimann and Hellman [8] allows that breast cancers indeed display a wide range of clinical behaviour, extending from those destined to remain localised to those that are disseminated when first detected. This reflects an increase in malignant characteristics throughout the clinical evolution of the tumour, by a process of gene mutation, selection and amplification. However, in this model, local or regional tumour extensions (e.g. lymph-node involvement) can be both a marker for and a source of dissemination.

According to the spectrum hypothesis, timely local therapy would be expected to prevent progression to a metastatic phenotype in some cases, but certainly not all, thereby improving survival rates overall. To deny this concept is not only counter-intuitive, but also contrary to clinical observation. Convincing evidence comes from randomised trials of mammographic screening. Although screening has come under fire as a public health policy, the weight of scientific opinion holds that screening substantially reduces breast cancer mortality within a screened population [9]. This indicates that some tumours can be treated before acquisition of a metastatic phenotype that would have otherwise been destined to develop. Other evidence comes from adjuvant therapy trials. Not only has local failure been shown to be an independent predictor of distant metastasis, but hazard functions for metastatic disease in women suffering from local failure also attain peak values later in time than is the case in tumours that metastasise without first recurring locally [10]. This suggests a re-seeding process as a consequence of local failure. This phenomenon was difficult to reconcile with the ostensibly negative survival effects observed in early adjuvant radiotherapy trials.

The Early Breast Cancer Trialists' Collaborative Group has conducted extensive clinical trial overviews, which have greatly clarified the relationship between local control and survival [11]. This most recent overview showed conclusively that the threefold reduction in locoregional failure brought about by adjuvant radiotherapy led to a significant reduction in mortality due to breast cancer. In absolute terms, the observed 20% improvement in local control was associated with a 5% increase in long-term, disease-specific survival. This implied that, for every four locoregional recurrences prevented, one breast cancer death could be avoided. These overviews have also explained why many older trials failed to reveal a beneficial effect of postmastectomy irradiation. First, as radiotherapy presumably improves survival by reducing metastatic re-seeding, this effect is delayed in time, with no benefit at all apparent during the first 5 years [11]. Older trials, most of which were not only statistically underpowered, but often also had insufficient follow-up, provided only unreliable evidence. In addition, most women in older trials received no systemic treatment, whereas risk-adapted chemotherapy, hormonal therapy, or both, is the current standard for